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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/942,121	08/30/2001	Zvi Sidelman	01/22453	6939

7590 03/08/2006

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,121	SIDELMAN, ZVI	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-294* is/are pending in the application.

4a) Of the above claim(s) *1-12,65-96 and 101-283* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-64,97-100 and 284-297* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. PCT/IL01/00198.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *see Attachment A*.

DETAILED ACTION

Status of the claims

Claims 1-283 are pending.

The amendment filed 11/29/05, which amended claims 14, 18, 26, 38, 46, 54, 57-58, 50, 53-54, 57-58, 61-62 and 97-98, and adds claims 284-297 has been entered. New claims 284-294 are drawn into the elected invention; and thus claims 13-64, 97-100 and 284-297 are examined in this Office action.

The terminal disclaimer filed 11/29/05 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of US Application Nos. 10788400 has been reviewed and are accepted.

Please note that ground of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Foreign priority

The current application claims that this application is a CIP of PTC/IL01/00198 (198) filed 3/1/2001, which does not disclose the amino acid sequence of instant SEQ ID NO:4 (RPKHP). The sequence of SEQ ID NO:4 of application 198 is instant SEQ ID NO:7. In light of that, the elected invention is directed to the methods of inducing hematopoiesis and the relatives thereof using peptide having the instant SEQ ID NO:4, the following claims under examination drawn to said peptide comprising the instant SEQ ID NO:4 are not granted benefit of the filing date 3/1/2001 of the parental application PTC/IL01/00198 (see attachment A).

Election/Restrictions

The response discusses the additional election of the peptide sequences of SEQ ID NOs:1-25, and submits that each sequence represents a species of a single genus (see pages 39-40).

Applicants' argument is found to be not persuasive because, though the sequences are derived from N-terminus of α S1 casein, they are not related as species from one another in structure and function, because dipeptide (Arg-Pro) of SEQ ID NO:1 is structurally distinct from SEQ ID NO:25 consisting of 25 amino acids which form secondary structure (see Alamino et al. (2000) *Biochim. Biophys. Acta.,* 1431, 410-420) whereas dipeptide in general does not so. Thus, the peptides of SEQ ID NOs:1-25 are structurally and/or functionally distinct/different from one another. The requirement of the additional election under 35 USC 121 in the Office action mailed 7/1/04 is proper. Therefore, the requirement is therefore still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-15, 17-19, 21-23, 25-27, 29-31, 33-35, 37-40, 41-43, 45-47, 49-51, 53-55, 57-59, 61-63 and 97-99 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention*. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

(1) Physical and/or chemical properties:

The current claims and specification do not provide the corresponding amino acid sequence with the corresponding SEQ ID NO:_ for α S1 casein polypeptide. There are various

forms of α S1 casein from different organisms which are distinct/different in amino acid sequence and/or biological function, e.g., the α S1 casein polypeptide (Accession No. P198228, consisting of **313** amino acids) form mouse and that from bovine (Accession No. NP_851372, consisting of **214** amino acids [see the attachment 1]) structurally differs from each other. As for as the N-terminal sequence (residues 1-25 of *mature* polypeptide) concerned, the bovine sequence (NP_851372) consists of "RPKHPIKHQGLPQEVLNENNLLLRFFV" whereas the mouse sequence (P198228) consists of MPRLHSRNAVSSQTQQQHSSSEEIF"; these two sequence (N-terminal residues 1-25) has only **4%** sequence identity. Because of this manifest structural diversity, the specification has to provide definitive peptide sequences in order for the skilled artisan to practice the claimed invention without undue experimentation.

The current disclosure is salient in teaching which N-terminal peptide of the mature α S1 casein polypeptide from an particular organism. One skilled in the art would not know how to make the N-terminal subsequence of an α S1 casein.

(2) Level of skill and knowledge in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to the amino acid sequence of α S1 casein. On paragraph [0134], the specification sets forth that "derived from an N terminus portion of oS1 casein" refers to cleavage products of α S1 casein, i.e., a peptides derived from natural casein, or a synthetic peptide chemically synthesized corresponding to the amino acid sequence of **an** N terminus portion of α S1 casein. The level of skill in this art is high and requires at least a molecular biologist and protein chemist with several years of experience in cloning and protein engineering as well as knowledge in peptide synthesis. Yet, even with a level of skill in the art as those

mentioned in precedence, predictability of the results (i.e., identifying active peptide fragments having activity such as hematopoiesis in claim 13) is still highly variable. An unduly level of skill is needed for the skilled artisan in order to develop the claimed method with the engineered peptide based on a full-length α S1 casein peptide/polypeptide.

(3) Functional characteristics:

Because is absent the primary structure of the claimed α S1 casein peptide which is necessarily required for one skilled in the art to practice the claimed invention, the functional characteristic of the N-terminal peptide from an full-length alpha casein cannot be determined and is not predictable.

(4) Method of making the claimed invention:

Since the disclosure fails to teach the amino acid sequence that identify α S1 casein from certain organism, the specification needs to provide sufficient guidance to be considered enabling.

In addition, the specification neither describes the methods of preventing thrombocytopenia (claims 53-56), pancytopenia (claims 57-60), and granulocytopenia (claims 61-64) comprising administering to a subject a peptide comprising the N-terminal fragment/portion of the oS1 casein, nor provides animal model or/and example in this regard. Thus, applicants are not in possession of the claimed methods.

The specification does not adequately teach how to make effective prophylaxis of the mentioned disorder (e.g., thrombocytopenia) ,which is a disease state with a reduced platelet (thrombocyte) count. The specification teaches the synthetic peptide of an α S1 casein N-terminus (see page 83) enhances platelet reconstitution with an animal model. However, the

specification does not teach how to extrapolate data obtained from the platelet reconstitution study to the development of effective in vivo mammalian including human therapeutic prevention, commensurate in scope with the claimed invention. Therefore, it is unclear that the skilled artisan could predict the efficacy of the claimed α S1 casein N-terminal peptide. Hence, applicants are not in possession of the claimed methods.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The applicants' response to the rejection under 35 USC 112, first paragraph

The response filed 11/29/05 argues that on skilled in the art would readily identify, and be capable of using the N-terminus portion of any α S1 casein sequence in order to develop the claimed methods (see pages 44, the 5th paragraph). The applicants' argument is found to be unpersuasive because of the reason set forth above, and because the amino acid sequences , especially N-terminal subsequences, of α S1 casein polypeptides vary from organism to organism.

On page 45, the response argues that the specification has taught preventive method for disorder states, e.g., thrombocytopeinia, pancytopenia and granulocytopenia. The applicants; argument is found to be unpersuasive because of the reason stated above, and because nowhere does the specification teach/describe the working example nor animal model referring to the above-mention preventive method for the said disorders. Although the specification provides working example (page 83) for the synthetic peptide to enhance the platelet reconstitution in an animal model, the specification does not teach how to extrapolate data obtained from the said platelet reconstitution study to the development of effective *in vivo* mammalian including human therapeutic prevention for the disorder (e.g., thrombocytopeinia), commensurate in scope with the claimed invention. Therefore, it is unclear that the skilled artisan could predict the efficacy of the claimed αS1 casein N-terminal peptide. Hence, applicants are not in possession of the claimed methods.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 13-64, 97-100 and 284-297 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites "*a peptide derived from an N terminus portion of αS1 casein*"; the recitation is indefinite because, without sequence identifier, it is unclear that the said N-terminal portion refers to mature αS1-casein or the precursor thereof (see the attachment 1), and because

the N-terminal subsequences of the mature αS1-casein derived from different organisms are highly diverse (see the above statement). Similarly, see also claims 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61 and 97. The dependent claims are also rejected.

Claim 16 sets forth non-elected SEQ ID NOs: 1-3 and 5-25 which are drawn to non-elected invention; thus, re-writing the claim is advised in order to eliminate the subject matters which have been withdrawn from consideration by this Office action. Similarly, see also claims 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 100.

The applicants' response to the rejection under 35 USC 112, second paragraph

On page 47, the response filed 11/29/05 discusses the issue regarding the non-elected sequences (SEQ ID NOs: 1-3 and 5-25), and submits that the sequences are related each other as species and should not be withdrawn from consideration. The applicants' argument is found to be unpersuasive because the reasons stated in the above section under "Election/restriction", and because the said sequences are structurally and/or functionally distinct/different from one another, and thus, are required additional election under 35 USC 121 which is NOT species election, as is clarified above thereof.

The rejection under 35 USC 102 is withdrawn in light of that the Enomoto et al. casein peptide is a precursor polypeptide, wherein the subsequence: Arg-Pro-Lys-His-Pro reads on the residues 1-5 of the mature polypeptide thereof but not residues 16-20; hence, the rejection falls. The applicant's argument in this regard is persuasive.

The provisional rejection - obviousness type double patenting is withdrawn in view of applicant having timely filed terminal disclaimer in compliance with 37 CFR 1.321(c).

Conclusion

No claims are allowed.

The following art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

• Saito et al. (2000, July) *J. Dairy Sci.* 83, 1434-1440) teach antihypertensive activity of peptide comprising Arg-Pro-Lys-His-Pro which reads on the instant SEQ ID NO:4.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The

examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Weber, Jon, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.
Art Unit 1653, Examiner
February 14, 2006

JON WEBER
SUPERVISORY PATENT EXAMINER

Attachment A from PCT/IL01/00198

SEQUENCE LISTING

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